Multimodal Medication Treatment in Refractory Neuropathic Pain, such as CRPS

대구파티마병원 재활의학과

박 동 휘

What is CRPS? Budapest Diagnostic Criteria of CRPS

1. Continuing pain that is disproportionate to any inciting event.

2. Must report at least one symptom in three of the four categories:

a. **Sensory:** hyperesthesia and/or allodynia

b. **Vasomotor:** temperature asymmetry and/or skin color changes and/or skin color asymmetry

c. **Sudomotor/edema:** reports of edema or sweating changes and/or sweating asymmetry

d. **Motor/trophic:** decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

3. Must display at least one sign in two or more of the following categories:

a. **Sensory:** hyperalgesia to pinprick, allodynia to light touch and/or deep somatic pressure and/or joint movement

b. **Vasomotor:** evidence of temperature asymmetry and/or skin color changes and/or asymmetry

c. **Sudomotor/edema:** evidence of edema and/or sweating changes an/or sweating asymmetry

d. **Motor/trophic:** evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

4. No other diagnosis that better explains the signs and symptoms.

Budapest Diagnostic Criteria of CRPS

Quantitative sensory test; **QST**

Quantitative sudomotor axon reflex test, **QSART**

기록지 작성일 / 생성일

복합부위통증증후군의 진단 기준

환자번호		이름		성별		생년월일	

임상 증상 및 증후	해당	비해당	필수 검사
복합부위통증증후군을 야기시킬 수 있는 침해성 요인 (inciting event)들이나, 사지 고정 등의 병인이 확실히 있어야 하며, 이러한 통증은 어떠한 침해성 요인과도 불균형 (disproportionate) 적이어야 한다.	☐	☐	
최초 수상일	년 월 일		
최초 증상 발생일	년 월 일		
다른 특정 질환 (PHN, DM neuropathy) 등에 의한 증상	☐	☐	
증상(symptom)			
(1) 감각이상 ☐ 감각 과민 ☐ 이질통	☐	☐	
(2) 혈관 이상혈관 확장 또는 수축 ☐ 혈관 확정 또는 수축 ☐ 피부 온도의 비대칭 ☐ 피부색의 변화	☐	☐	
(3) 부종 또는 발한 이상 ☐ 부종 ☐ 다한증 또는 저한증	☐	☐	
(4) 운동 또는 이영양성 변화 ☐ 운동 가동역 감소 ☐ 운동 부전 ☐ 손발톱 또는 모발의 변화 ☐ 피부위축 또는 피부 이영양성 변화	☐	☐	

징후(sign)			
(1) 감각 이상 ☐ 감각 과민 ☐ 이질통	☐	☐	☐ NRS ☐ EMG/NCS ☐ QST
(2) 혈관 이상 ☐ 혈관 확정 또는 수축 ☐ 피부 온도의 비대칭 ☐ 피부색의 변화	☐	☐	☐ 삼상 골스캔 ☐ 체열촬영 ☐ 사진촬영
(3) 부종 또는 발한 이상 ☐ 부종 ☐ 다한증 또는 저한증	☐	☐	☐ 사진촬영(필수) ☐ 의무기록지(필수) ☐ 단순방사선 ☐ 초음파 ☐ MRI ☐ QSART
(4) 운동 또는 이영양성 변화 ☐ 운동 가동역 감소 ☐ 운동 부전 ☐ 손발톱 또는 모발의 변화 ☐ 피부위축 또는 피부 이영양성 변화	☐	☐	☐ BMD ☐ CT 촬영 ☐ 사진촬영
해당되는 증상 및 증후 범주의 총 개수			
(1) 증상 : 4범주 중 총 ( ) 범주에 해당 (2) 징후 : 4범주 중 총 ( ) 범주에 해당			

Pathophysiology of CRPS

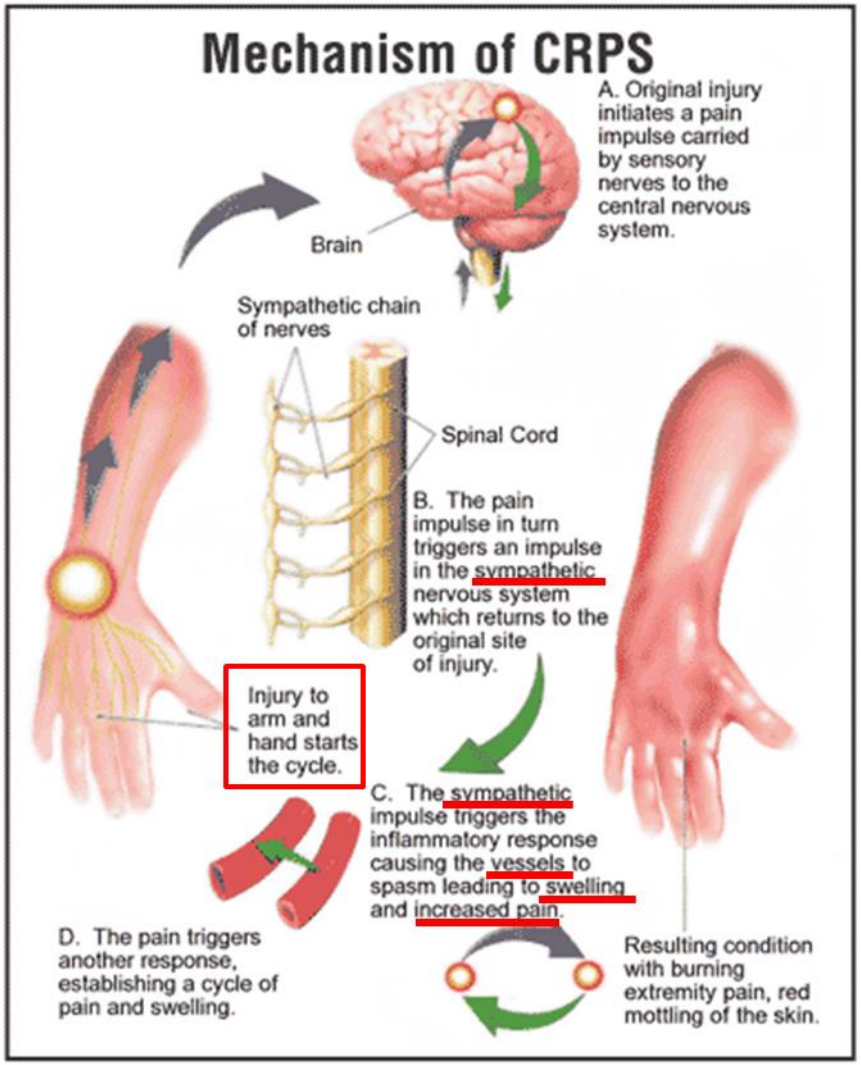


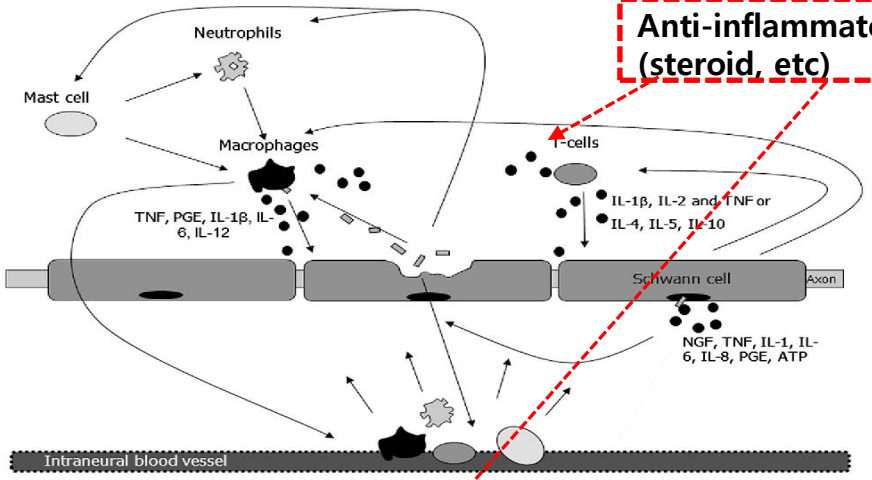
Figure 1. The exact mechanism of complex regional pain syndrome (CRPS) is unclear. This depicts a simplified version of how an injury might result in the symptoms associated with CRPS.

1. **Peripheral nerve injury**
   - 근전도 positive : CRPS type 2
   - 근전도 negative : A-δ or C-fiber
2. **Peripheral sensitization**
3. **Central sensitization**
4. **Trigger Sympathetic nervous system**
5. **Neuro-inflammation**
   - microglia, astrocyte
6. **Basal ganglia dysfunction**
   - dopamine pathway, dystonia
7. **Auto-immunity**
8. **Endothelial dysfunction**

Acute phase of CRPS : Inflammation control

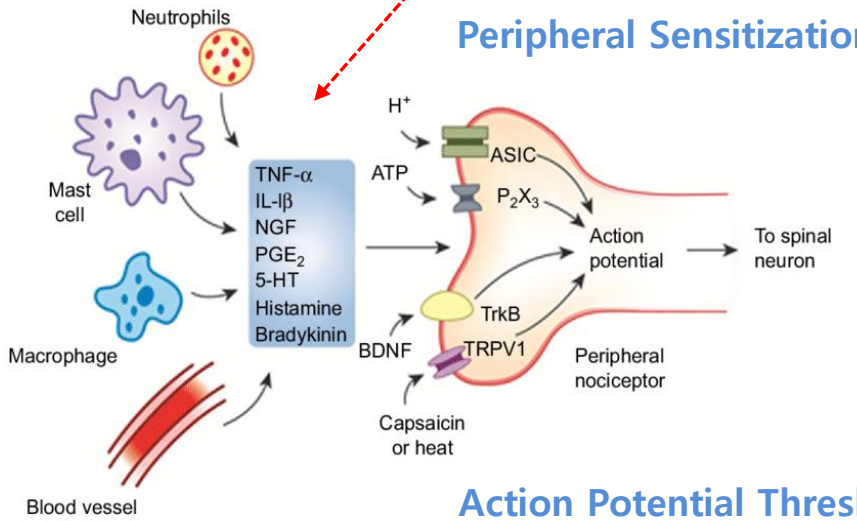
Peripheral Nerve Injury (A-δ or C-fiber); large-diameter nerve injury와 동반 유무

Anti-inflammatory agent (steroid, etc)



Central Sensitization

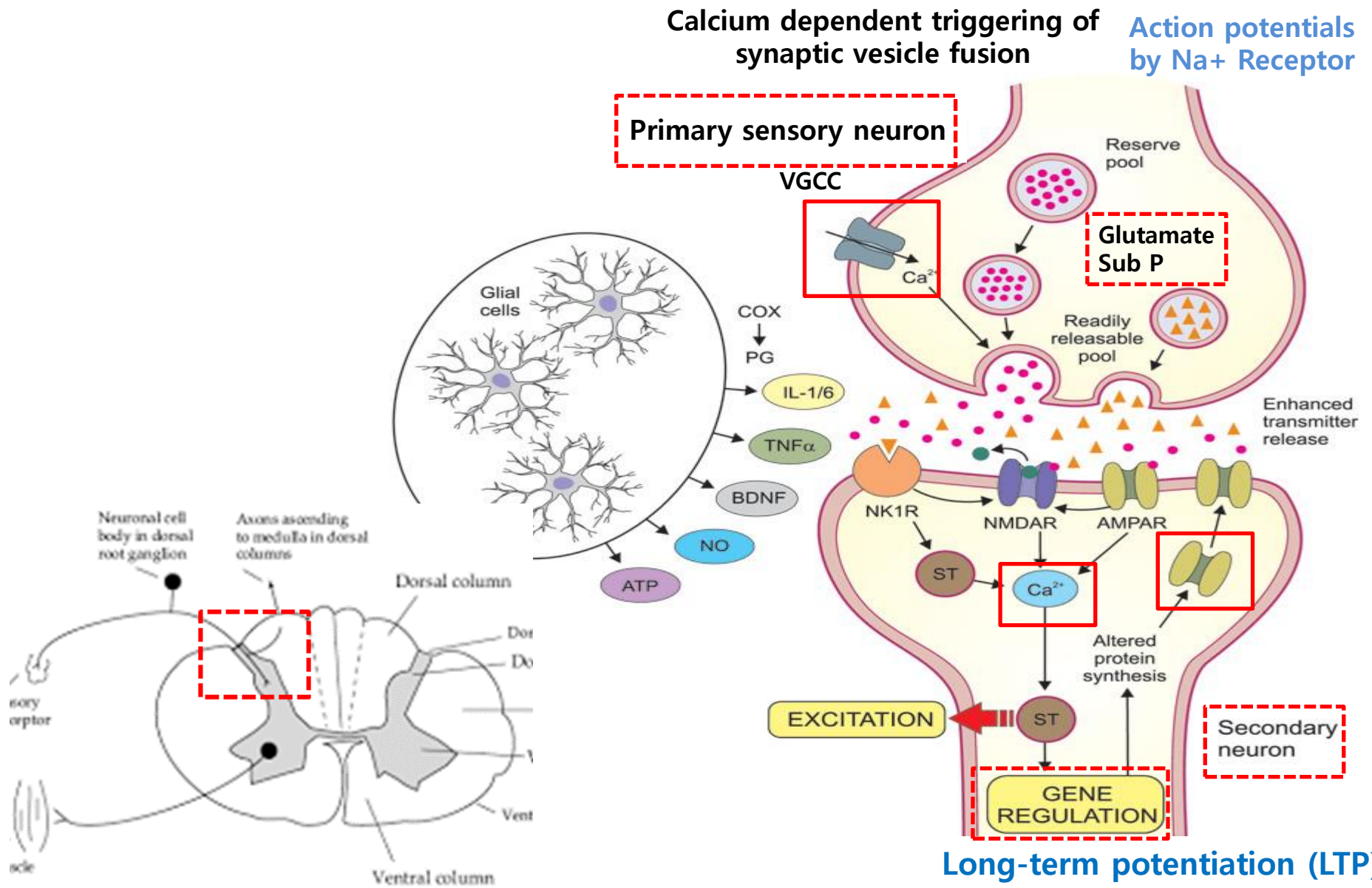
Peripheral Sensitization



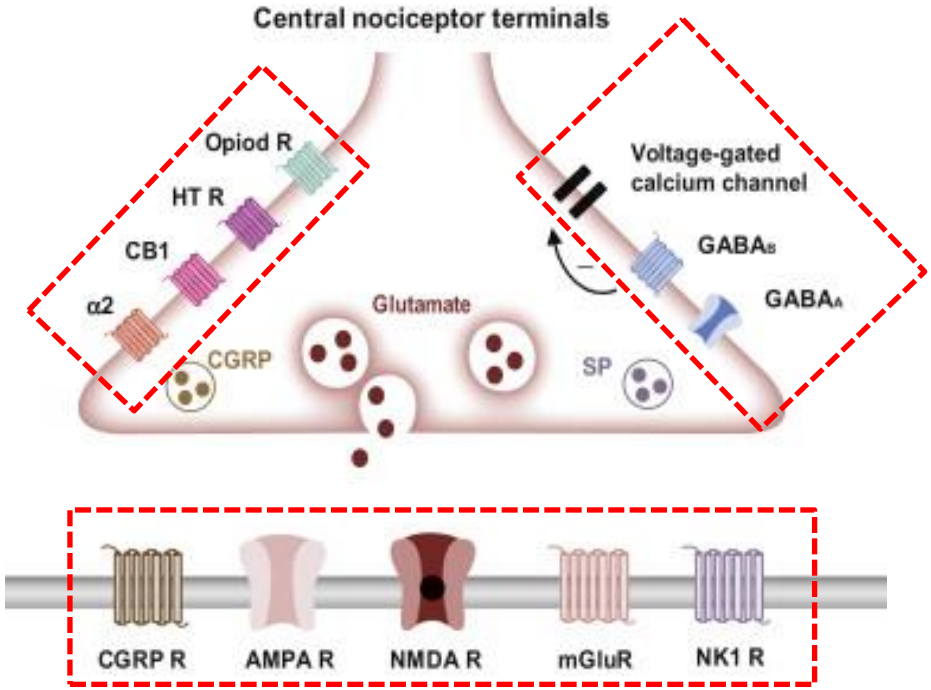
Action Potential Threshold 감소

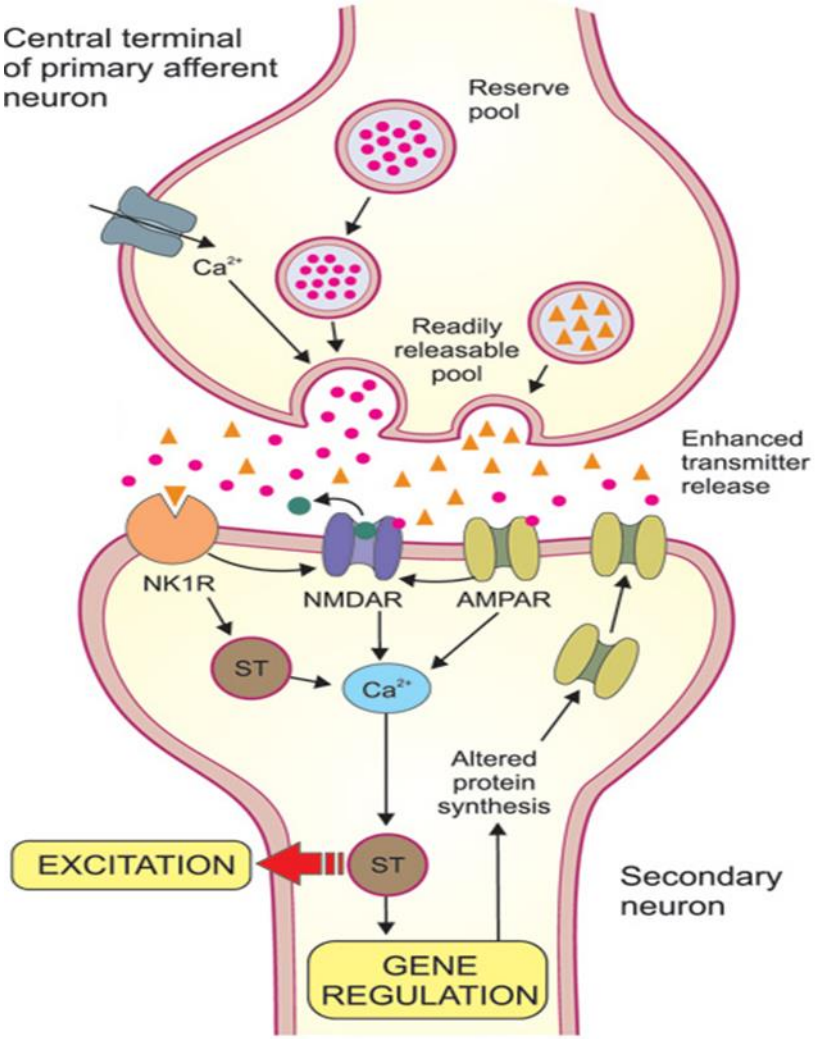
Action Potential Threshold 감소

Central sensitization (Neuroinflammation + LTP)



Central Sensitization : Long-Term Potentials (LTP)





Neuropathic pain; Neuropathic pain symptom inventory (NPSI)

부록 1. 한국어 신경병통증 설문지

이름 :　　작성일:

통증에 대한 감별 및 평가를 위한 질문들입니다. **지난 일주일 동안** 귀하가 느끼는 통증에 해당하는 질문이면 **예**로 답하시고 그렇지 않으면 **아니요**로 답하십시오. **예**로 답하신 경우에는 그 정도를 표시하여 주시기 바랍니다.

1. 핀이나 바늘로 찌르듯 따끔거리는 통증입니까? 예 아니오
   찌르는 듯한 통증 없음 — 0 1 2 3 4 5 6 7 8 9 10 — 상상할 수 있는 최악의 찌르는 듯한 통증
2. 칼이나 송곳으로 후벼파는 듯한 통증입니까? 예 아니오
   후벼파는 듯한 통증 없음 — 0 1 2 3 4 5 6 7 8 9 10 — 상상할 수 있는 최악의 후벼파는 듯한 통증
3. 전기 오르듯이 찌릿찌릿한 통증입니까? 예 아니오
   찌릿찌릿한 통증 없음 — 0 1 2 3 4 5 6 7 8 9 10 — 상상할 수 있는 최악의 찌릿찌릿한 통증
4. 화끈거리는 통증입니까? 예 아니오
   화끈거리는 통증 없음 — 0 1 2 3 4 5 6 7 8 9 10 — 상상할 수 있는 최악의 화끈거리는 통증
5. 시린 통증입니까? 예 아니오
   시린 통증 없음 — 0 1 2 3 4 5 6 7 8 9 10 — 상상할 수 있는 최악의 시린 통증
6. 뻐근하거나 묵직한 통증입니까? 예 아니오
   뻐근하거나 묵직한 통증 없음 — 0 1 2 3 4 5 6 7 8 9 10 — 상상할 수 있는 최악의 뻐근하거나 묵직한 통증
7. 꽉 죄는 듯한 통증입니까? 예 아니오
   꽉 죄는 듯한 통증 없음 — 0 1 2 3 4 5 6 7 8 9 10 — 상상할 수 있는 최악의 꽉 죄는 듯한 통증
8. 눌리는 듯한 통증입니까? 예 아니오
   눌리는 듯한 통증 없음 — 0 1 2 3 4 5 6 7 8 9 10 — 상상할 수 있는 최악의 눌리는 듯한 통증
9. 통증 부위가 가볍게 닿아도 통증이 유발되거나 악화됩니까? 예 아니오
   닿을 때 통증 없음 — 0 1 2 3 4 5 6 7 8 9 10 — 닿을 때 상상할 수 있는 최악의 통증
10. 누르면 통증이 유발되거나 악화되었습니까? 예 아니오
    누를 때 통증 없음 — 0 1 2 3 4 5 6 7 8 9 10 — 누를 때 상상할 수 있는 최악의 통증
11. 차가운 것이 닿으면 통증이 유발되거나 악화됩니까? 예 아니오
    차가운 것이 닿을 때 통증 없음 — 0 1 2 3 4 5 6 7 8 9 10 — 차가운 것이 닿을 때 상상할 수 있는 최악의 통증
12. 피가 안 통할 때처럼 저리는 통증입니까? 예 아니오
    저리는 통증 없음 — 0 1 2 3 4 5 6 7 8 9 10 — 상상 할 수 있는 최악의 저리는 통증
13. 통증부위가 치과에서 마취한 듯 남의 살 같거나 감각이 둔합니까? 예 아니오
    감각 둔함 없음 — 0 1 2 3 4 5 6 7 8 9 10 — 전혀 감각을 느끼지 못함
14. 면봉 등으로 건드리면 통증부위가 둔하게 느껴지거나 감각이 떨어집니까? 예 아니오
    감각 둔함 없음 — 0 1 2 3 4 5 6 7 8 9 10 — 전혀 감각을 느끼지 못함
15. 바늘 같은 뾰쪽한 물건으로 찌르면 통증부위가 둔하게 느껴지거나 감각이 떨어집니까? 예 아니오
    감각 둔함 없음 — 0 1 2 3 4 5 6 7 8 9 10 — 전혀 감각을 느끼지 못함
16. 통증부위가 벌레가 기어가는 듯하거나 가렵습니까? 예 아니오
    가려움 없음 — 0 1 2 3 4 5 6 7 8 9 10 — 상상할 수 있는 최악의 가려움
17. 통증부위를 만지면 더 아프게(예민하게) 느껴집니까? 예 아니오
    예민함 없음 — 0 1 2 3 4 5 6 7 8 9 10 — 상상할 수 있는 최악의 예민함
18. 통증부위의 피부색깔이 다른 정상부분과 다릅니까? 예 아니오
    다르지 않음 — 0 1 2 3 4 5 6 7 8 9 10 — 완전히 다름
19. 통증의 정도가 얼마나 심합니까? 예 아니오
    통증 없음 — 0 1 2 3 4 5 6 7 8 9 10 — 상상할 수 있는 최악의 통증
20. 통증 때문에 얼마나 힘들거나 불편합니까? 예 아니오
    불편하지 않음 — 0 1 2 3 4 5 6 7 8 9 10 — 상상할 수 있는 최악의 불편한 통증
21. 평소 견딜 수 없이 아파서 통증 때문에 일상생활에 지장을 받습니까? 예 아니오
    통증으로 인해 생활에 지장 없음 — 0 1 2 3 4 5 6 7 8 9 10 — 상상할 수 있는 최악의 일상생활 지장
22. 날씨에 따라 통증이 심해집니까? 예 아니오
    전혀 심해지지 않음 — 0 1 2 3 4 5 6 7 8 9 10 — 상상할 수 있는 한 최대로 심해짐
23. 통증이 관절에만 있습니까? 예 아니오
24. 지난 24시간 동안, 저절로 발생한 통증이 얼마나 오랫동안 지속되었습니까? (　　)
    ① 지속적으로 ② 8시간 이상에서 12시간 미만 ③ 3시간 이상에서 8시간 미만 ④ 1시간 이상에서 3시간 미만 ⑤ 1시간 미만
25. 지난 24시간 동안, 통증이 얼마나 자주 발생하였습니까? (　　)
    ① 21회이상 ② 11회에서 20회 사이 ③ 6회에서 10회 사이
    ④ 1회에서 5회 사이 ⑤ 통증이 없었다

Neuropathic pain; Evoked pain (Allodynia)

Touch Allodynia

Pressure Allodynia

Cold Allodynia

- **Allodynia** refers to **central pain sensitization** (increased response of neurons) following normally non-painful, often repetitive, stimulation.
- **Allodynia** can lead to the triggering of a pain response from stimuli which do not normally provoke pain.
- Touch allodynia (9), Pressure allodynia (10), Cold allodynia (11)

Neuropathic pain

Affiliations:

From the Departments of Rehabilitation Medicine (KM, YO) and Psychiatry (S-HL), CHA Bundang Medical Center, CHA University Seongnam-si, Gyeonggi-do, South Korea; and Department of Rehabilitation Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam-si, Gyeonggi-do, South Korea (JSR).

Correspondence:

All correspondence and requests for reprints should be addressed to: Ju Seok Ryu, MD, PhD, Department of Rehabilitation Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, 82 Gumi-ro 173 Beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do 463-707, South Korea.

Disclosures:

Supported by Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Science, ICT and Future Planning (NRF-2013R1A1A1004622).
This trial has been registered with the ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT02180880).
Financial disclosure statements have been obtained, and no conflicts of interest have been reported by the authors or by any individuals in control of the content of this article.

Editor's Note:

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.ajpmr.com).

0894-9115/16/9505-0330
American Journal of Physical

ORIGINAL RESEARCH ARTICLE

Symptom-Based Treatment of Neuropathic Pain in Spinal Cord-Injured Patients

A Randomized Crossover Clinical Trial

Evoked pain = allodynia

ABSTRACT

Min K, Oh Y, Lee S-H, Ryu JS: Symptom-based treatment of neuropathic pain in spinal cord-injured patients: a randomized crossover clinical trial. Am J Phys Med Rehabil 2016;95:330–338.

Objective: The objective of this study was to identify the differences in medication effect according to pain characteristics in spinal cord-injured patients.

Methods: This study is a prospective, randomized, crossover study. Fifty-five patients and 66 locations of neuropathic pain were included. Pain was classified into four spontaneous characteristics and three evoked pain characteristics. Oxcarbazepine (Na^+ channel blocker) and pregabalin (calcium channel α_2-δ ligand medication) were tried. Patients were divided into two groups: evoked pain present and evoked pain absent. Overall average visual analog scale was obtained.

Results: Oxcarbazepine was significantly more effective for patients without evoked pain than in those with it for electrical, burning, and pricking pain. The effect of pregabalin was not different regarding the presence or absence of evoked pain for all pain categories, except burning pain. In patients with evoked pain, pregabalin was shown to be significantly more effective for electrical pain, allodynia, and heat hyperalgesia than oxcarbazepine. In the evoked pain absent group, oxcarbazepine showed greater improvement than pregabalin but was not significant.

Conclusions: In summary, the phenotype of neuropathic pain was associated with the efficacy of different pharmacologic treatments. Symptom-based treatment, therefore, can lead to more efficient analgesia.

Key Words: Neuralgia, Spinal Cord, Oxcarbazepine, Pregabalin, Drug Therapy, Symptom Assessment

Management of CRPS

Multimodal Medication Therapy

전제

1. CRPS 에서 Acute phase 에서의 main pathophysiology neuroinflammation 이다 (peripheral & central neuroinflammation).

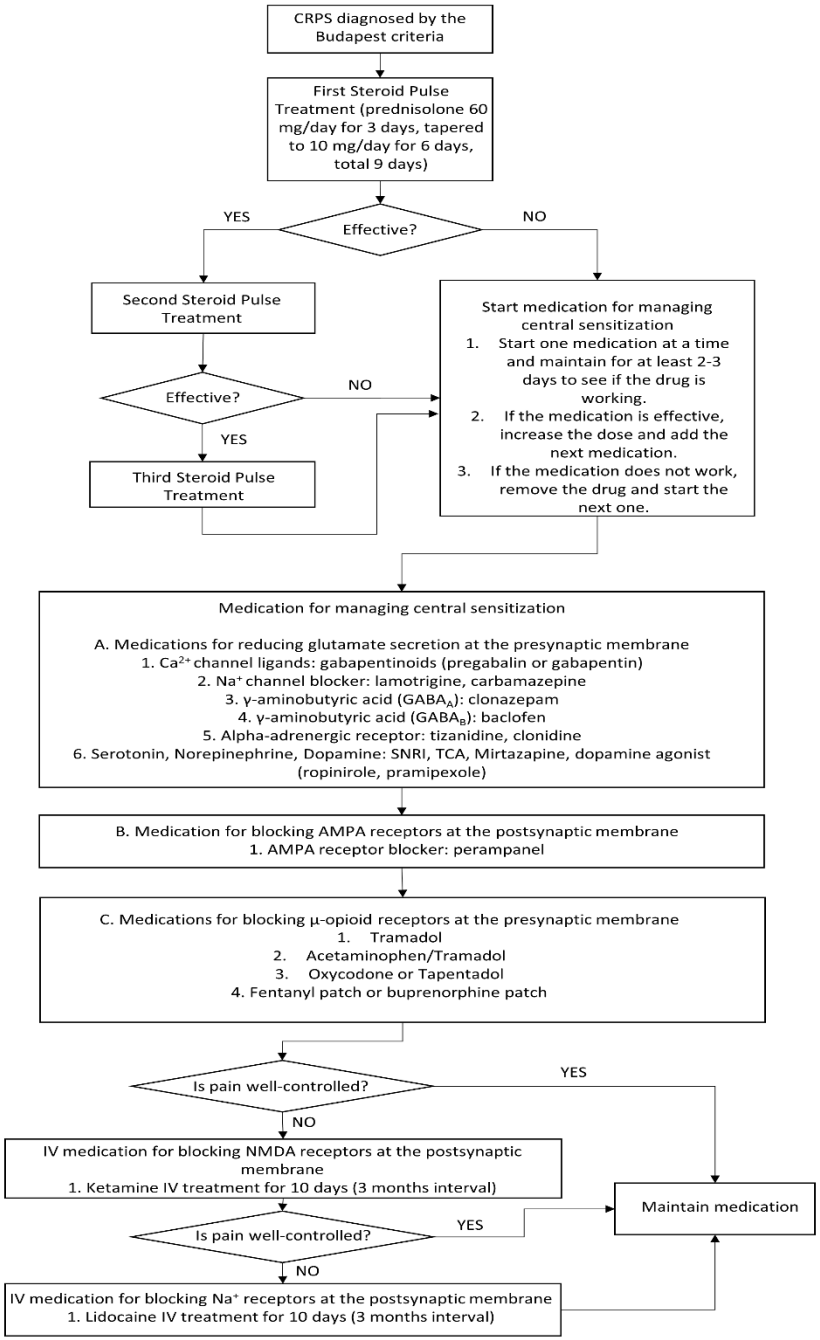
2. 그 이후에는 neuroinflammation이 아닌, long-term potentiation (LTP) 에 의한 central sensitization이 주된 pathophysiology 가 된다.

3. LTP를 막기 위해서는 pre-synaptic sensory neuron에서 substance P, glutamate 와 같은 neurotransmitter의 분비를 최소화해야 한다.

4. LTP를 막기 위해서는 post-synaptic sensory neuron에서 NMDA, AMPA Rc 와 같은 수용체의 activation 을 최소화해야 한다.

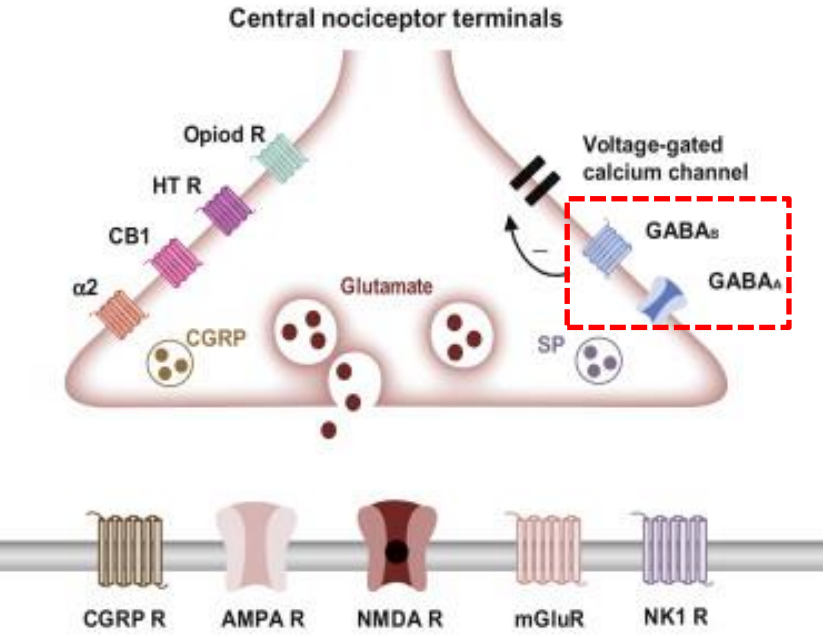
5. 사람마다 CRPS의 통증양상이 다 다르듯, 발현된 주된 수용체도, 수용체의 발현정도도 다를 것이다 -> 개별적 치료 (multimodal medication therapy)의 필요성.

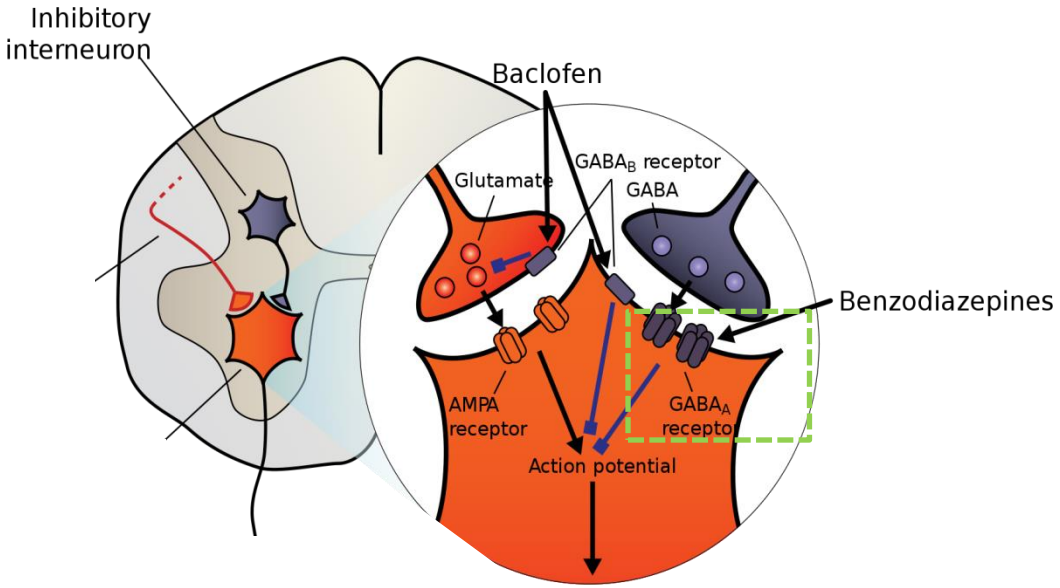
Algorithm of Multimodal Medication Therapy



Pharmacologic options for CRPS: Pre-synaptic

①**Baclofen** (Prex®, $GABA_B$ A) or **Clonazepam** (Rivotril® $GABA_A$ A)
Diazepam (Valium® $GABA_A$ A)
Midazolam IV ($GABA_A$ A)





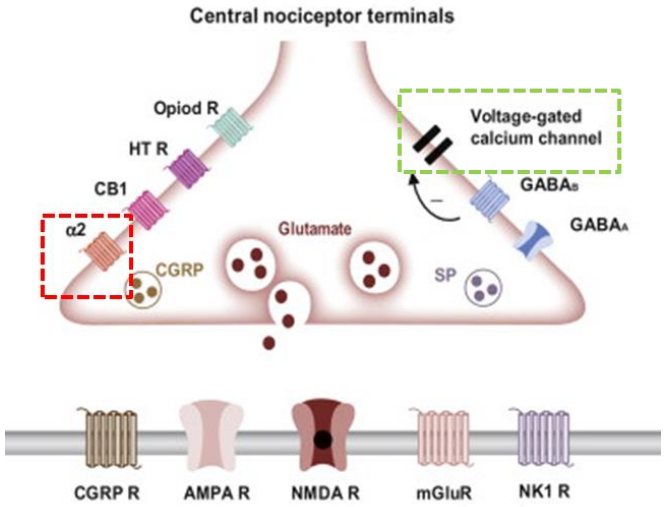
Pharmacologic options for CRPS

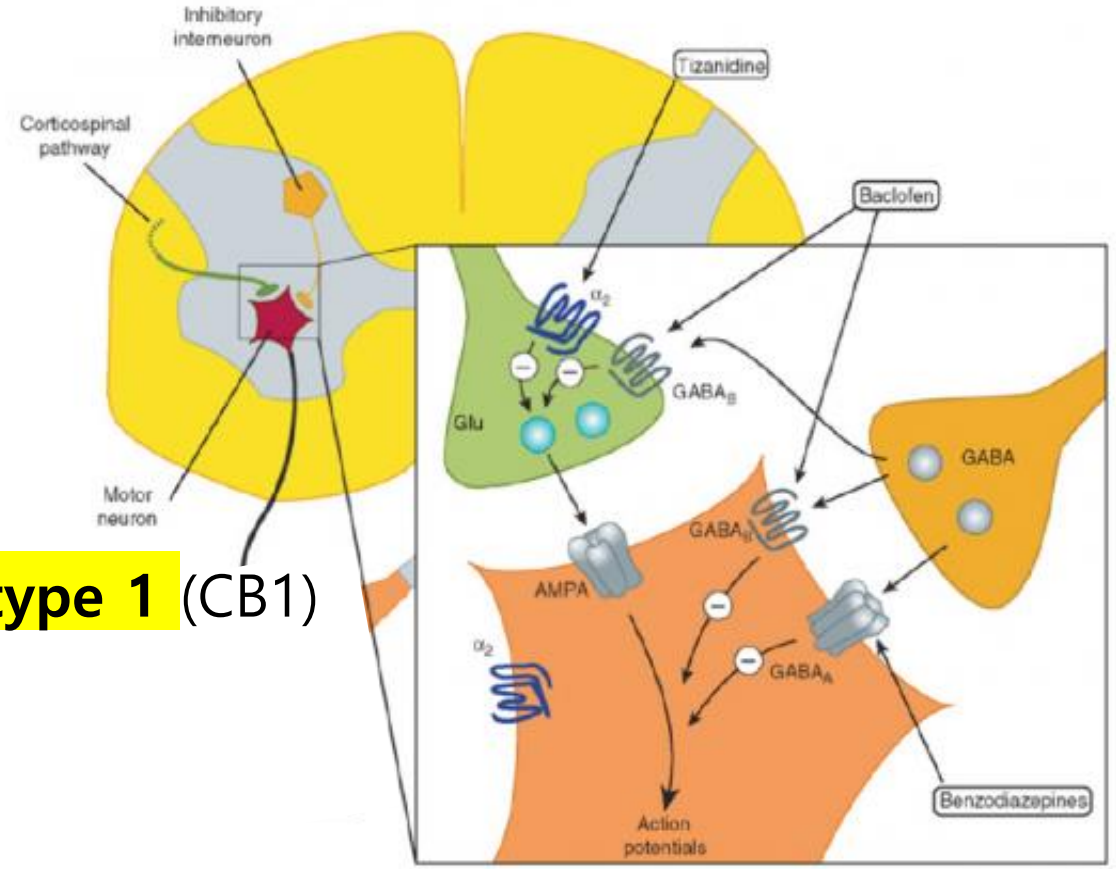
② **Tizanidine** (**Sirdalud®**), **Clonidine** (**Kapvay®**)

- Centrally acting α2 adrenergic agonist

③ **Gabapentinoids** (**Gabapentin** or **Pregabalin**)

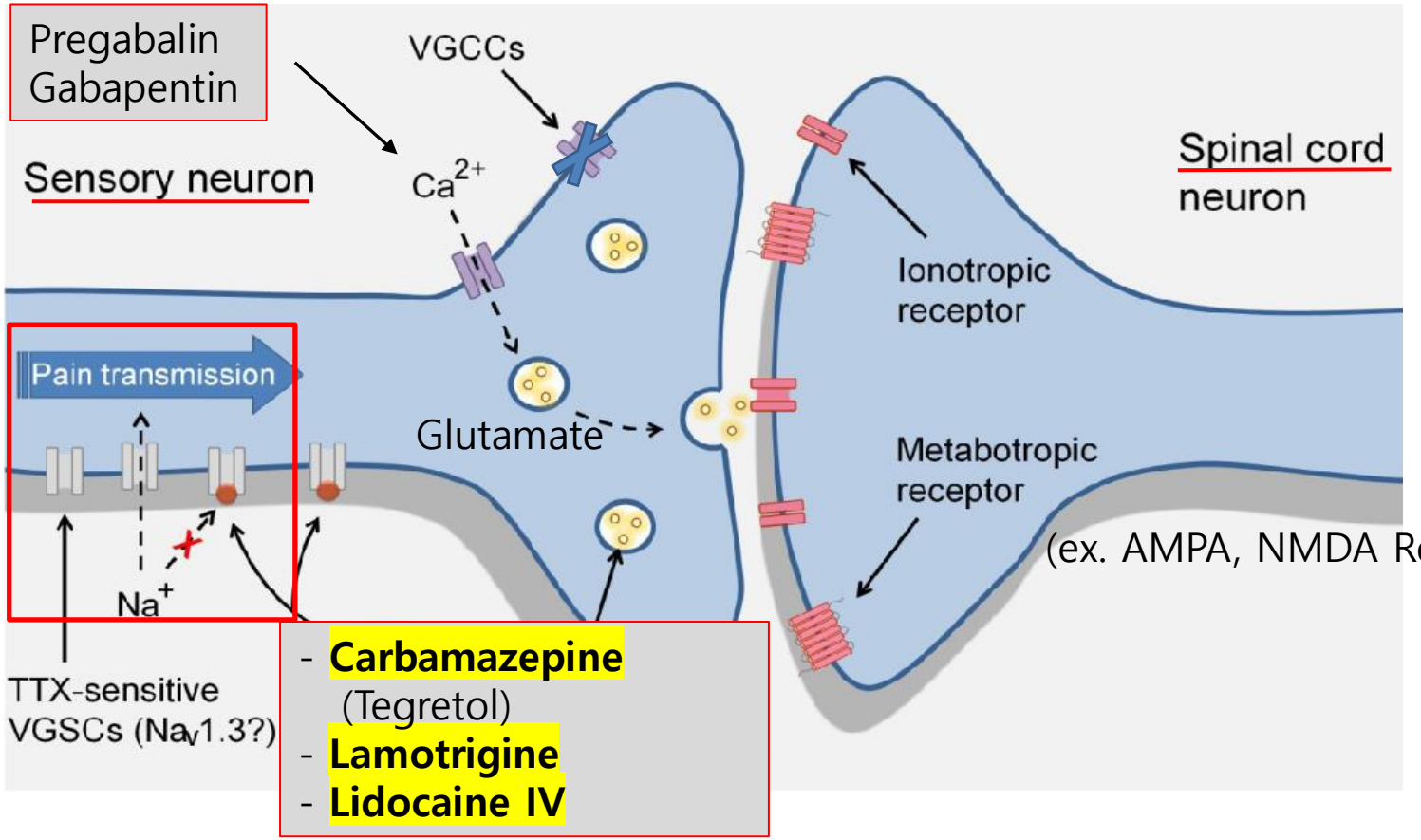
- Inhibitor of **α2δ subunit-VGCC**





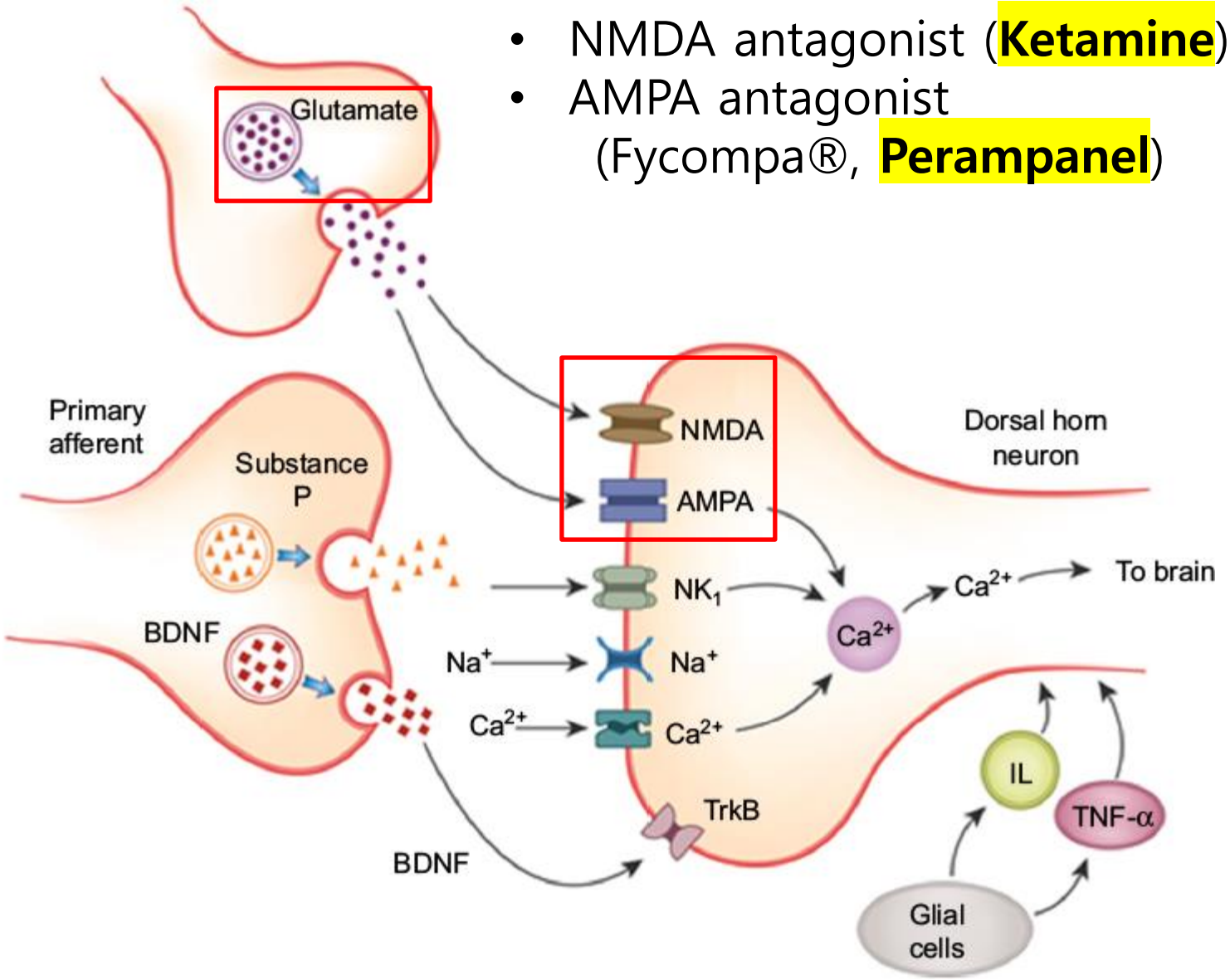
④ **Cannabinoid receptor type 1** (CB1)

Pharmacologic options for CRPS



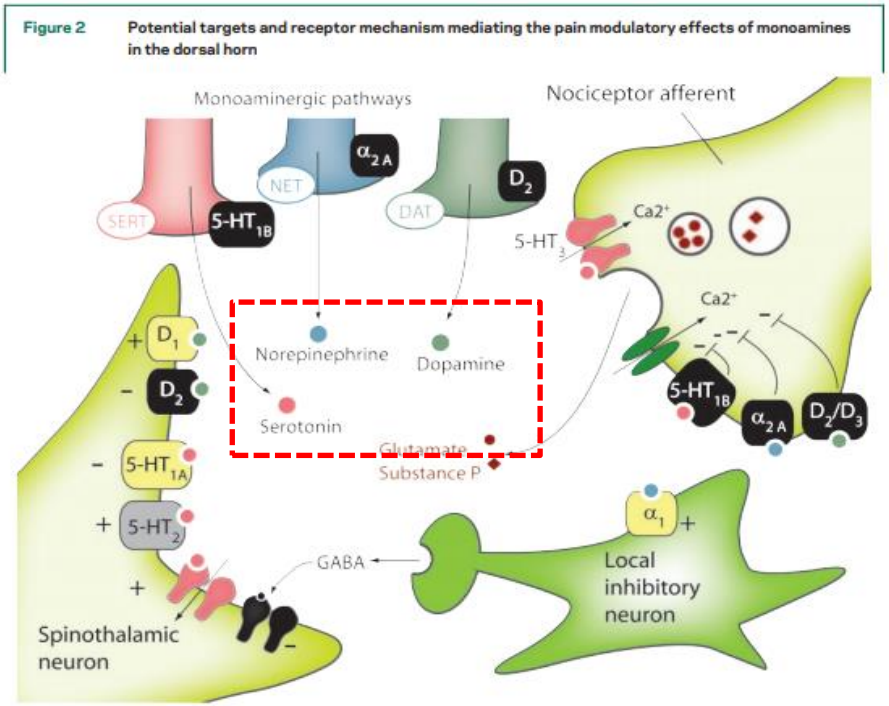
Pharmacologic options for CRPS: Post-synaptic

- NMDA antagonist (**Ketamine**)
- AMPA antagonist
  (Fycompa®, **Perampanel**)



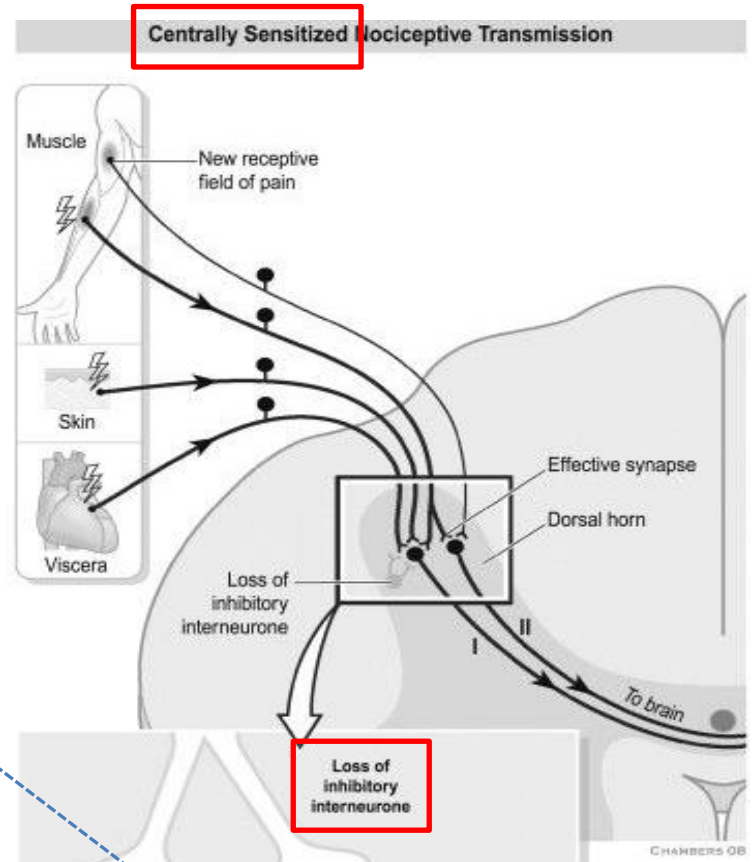
Pharmacologic options for CRPS (inhibitory inter-neuron)

- SSRI (Fluoxetine; Prozac®) (not recommended)
- SNRI (**Velnafaxine**; Efexor®, **Duloxetine**; Cymbalta®)
- **Mirtazapine** (increase secretion of Norepi & Serotonin)
- **TCA** (Amitriptyline: strong action on serotonin transporter and moderate effects on norepinephrine transporter)
- Dopaminergic agonist? (ropinirole; Requip®, pramipexole ;Mirapex®)

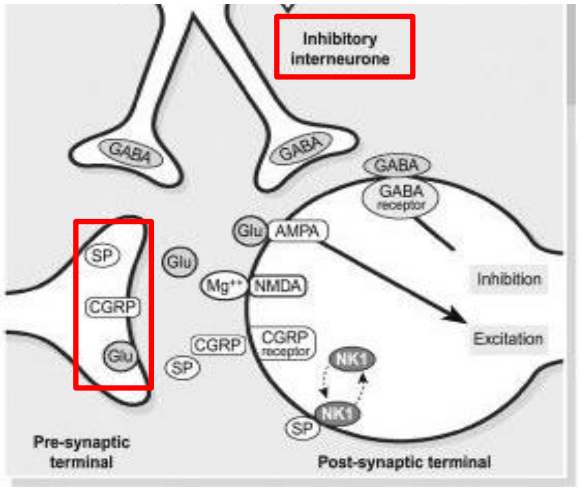


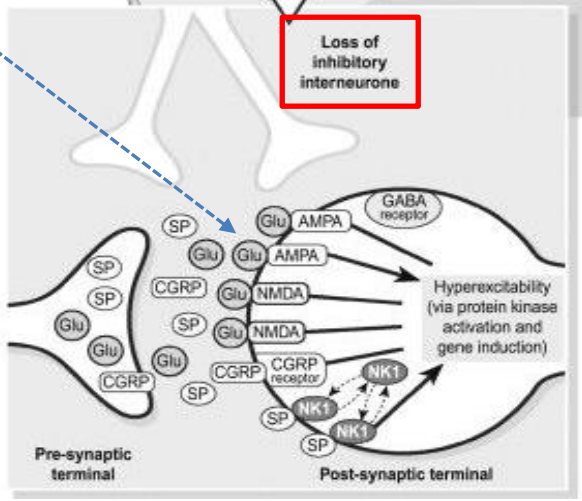
Process of neuropathic pain

1. **Peripheral sensitization** (**inflammation**)
   -Threshold 감소, AP 생성
   -AP의 비정상적인 증가 (**Na^+ Rc 증가**)
2. **Central sensitization**
   - increased NT (SubP, CGRP, Glut)
   - **neuroinflammation (Glia)**
   - **post synaptic AMPA receptor 의 증가**
   - **inhibitory interneuron의 loss**



Long-term potentiation (LTP)





Ketamine IV for NMDA Receptor Block at Post-synaptic mb

- The therapeutic range of ketamine makes it one of the safest sedative agents for most emergency clinical and preclinical situations.
- In low doses, it causes analgesia and sedation, and in high doses, it produces general anesthesia.
- Time of onset: 30s, Duration of Action after dosing: 5-10 min for bolus dose
- Ketamine's half-life in plasma is approximately 2.3 ± 0.5 hours.
- Currently, three pain societies recommend intravenous dosing of ketamine for chronic pain at 0.5 to 2 mg/kg for one-day outpatient or three- to five-day inpatient awake treatment with higher doses titrated to effect.

Ketamine IV 입원치료 Protocol

본원 Protocol (입원)

Ketamine IV: 5 +2 (휴지기) + 5

0.35mg/kg/hour (1.4mg/kg) for 4 hours 를 maximum dose 로 하고
1일차 maximum dose 의 50%
2일차 maximum dose 의 75%
3일차 maximum dose 의 100%

- 25mg/hour 를 넘지 않게 N/S 100 mL 에 mix 해서 4시간 동안 준다.

- Unpleasant visual hallucination, nightmare 와 같은 high dose ketamine 부작용을 예방하기 위해 **시작 전** midazolam 2mg IV, ketamine 치료 시작 **4시간 후** midazolam 2mg IV 를 같이 해준다.

- 약물에 대한 내성을 방지하기 위해 3개월이상의 term 을 두고 시행한다.

- With nasal O_2 (2L), O_2 Satuation monitoring, Flumazenil 0.5mg (상비)

Lidocaine IV 치료 Protocol for Na+ Rc Block

본원 Protocol (입원)

Lidocaine IV:

2% lidocaine을 용량 계산하여 normal saline 500mL 에 mix 하여 4시간동안 준다.
1일차 1mg/kg
2일차 2mg/kg
3일차 5mg/kg

- Maximum 5mg/kg 로 하여, side effect (dizziness, nausea..)가 없는 최대한의 범위로 올려준다. With EKG monitoring.

- Dizziness 등 부작용이 있을 경우 바로 전 dose로 준다.

- Midazolam 2mg 전 후 해주기도 함.

- With nasal O_2 (2L), O_2 Satuation monitoring, Flumazenil 0.5mg (상비)

- 대부분 Ketamine IV 할 때 sedation이 문제가 되는 사람들은 midazolam 없이

Pain Medicine

PAIN MEDICINE
Volume 10 • Number 2 • 2009

Preliminary Research Articles

Efficacy of 5-Day Continuous Lidocaine Infusion for the Treatment of Refractory Complex Regional Pain Syndrome

Robert J. Schwartzman, MD, Mona Patel, MD, John R. Grothusen, PhD, and Guillermo M. Alexander, PhD

Department of Neurology, Drexel University College of Medicine, Philadelphia, Pennsylvania, USA

ABSTRACT

Objective. Chronic regional pain syndrome (CRPS) is a severe pain condition that usually results from an injury or surgical procedure. The pain in CRPS often spreads from the site of injury, and with time becomes refractory to conventional therapy. The present study was undertaken to evaluate the effects of 5-day continuous intravenous lidocaine treatment in patients afflicted with CRPS.

Methods. Intravenous lidocaine was administered in an escalating dose schedule to 49 severely affected CRPS patients in a monitored setting over 5 days. Evaluation of pain parameters and other signs and symptoms of CRPS were obtained during the infusion and at 1, 3, and 6 months following therapy.

Results. The majority of patients demonstrated a significant decrease in pain parameters and other symptoms and signs of CRPS. The pain reduction lasted an average of 3 months. Lidocaine may be particularly effective for thermal and mechanical allodynia. Less clinically significant effects were documented on the motor aspects of the syndrome.

Discussion. Intravenous lidocaine administration titrated to 5 mg/L demonstrated: 1) a significant decrease in mechanical and thermal allodynia for three months, 2) lessened associated inflammatory components of CRPS, and 3) only minimal side effects and no severe complications.

Key Words. Refractory CRPS; Lidocaine; Thermal Allodynia; Mechanical Allodynia; Complex Regional Pain Syndrome

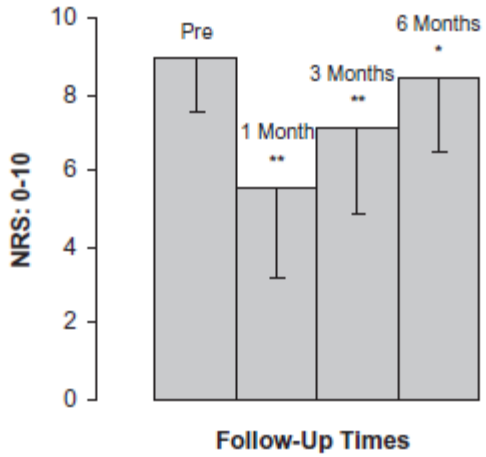


Figure 1 Overall pain intensity. This figure illustrates the reported overall pain as mean ± SD before and at 1, 3, and 6 months following 5 days of intravenous lidocaine infusion, rated on an NRS scale of 0–10. Statistical significance was evaluated with a paired *t*-test (* $P < 0.05$; ** $P < 0.005$). NRS = numerical rating scale.

2% Lidocaine 1cc = 20mg Lidocaine
2g Lidocaine = 2% lidocaine 100cc

Treatment Protocol

All patients were monitored in a step-down unit. Blood pressure, EKG, and oxygenation were monitored in standard fashion.

Lidocaine infusion consisted of 2 g of lidocaine in 250 mL of 5% dextrose in water delivered by continuous infusion at a rate of 7.55 cc/h (60.4 mg/h) over the first 24 hours, 11 cc/h over the next 24 hours, 15 cc on day 3, 18 cc/h on day 4, and 21 cc/h (168.0 mg/h) on day 5. Blood lidocaine levels were obtained daily (Table 5), and the infusion rate increased only if the blood level was less than 5 mg/L. If the blood lidocaine level was greater than 5 mg/L, the rate of infusion was decreased to the rate used on the previous day. If side affects occurred, drop in blood pressure, cardiac arrhythmia, dysphoria, or dizziness, dosage was decreased or stopped. This 5-day treatment protocol was designed after successful treatment of eight previous patients. These patients responded successfully to a titrated maximal infusion rate of 21 cc/h (168.0 mg/h). Faster infusion rates and longer than 5 days of treatment caused dizziness, dysphoria, and hypotension.

Complications

The side effects were mild, and no severe complications were noted. Sixteen of 49 (32.6%) patients had side effects. The mild side effects included nausea (N = 1), fatigue (N = 1), bradycardia (N = 2), tachycardia (N = 1), atrial arrhythmia (N = 1), and hypotension (N = 2). As soon as cardiac complications were noted, the treatment was stopped. Psychiatric side effects included disorientation (N = 1), euphoria (N = 3), hallucinations and nightmares (N = 1). These complications occurred at a dose of 15–18 cc/h (120–144 mg/h). One patient suffered a seizure, one vertigo, and one suffered blurred vision. All side effects disappeared within 12 hours of cessation of treatment, and no long-term effects were noted in any patient.

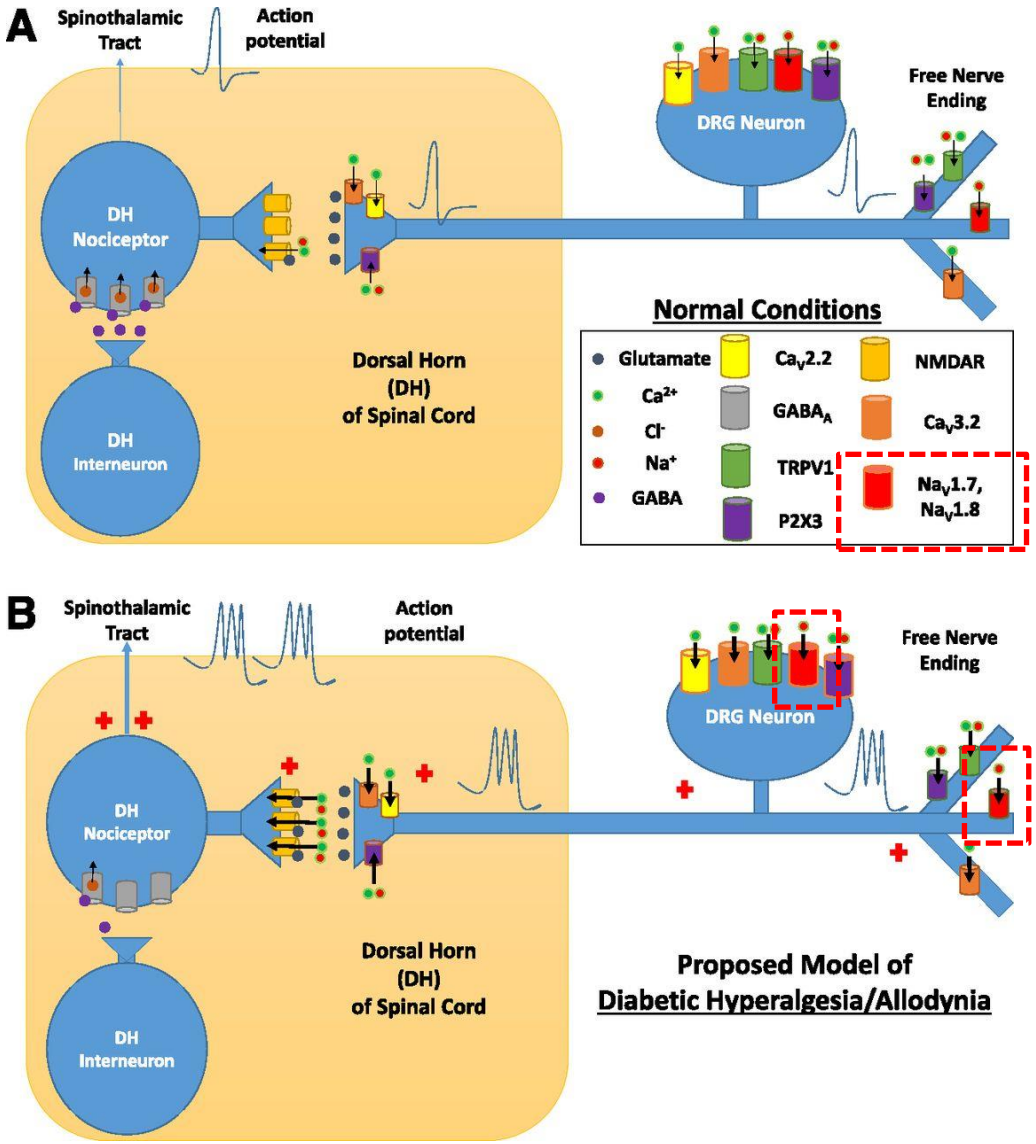
- Peripheral nerve injury may maintain a central hyperexcitable state by continual spontaneous discharge due to an abnormal concentration of sodium channels in the injured nerve trunk or its terminal twigs [1].

- Treatment with lidocaine and SP and CGRP antagonists delayed the onset of neuropathic pain by 1–4 days compared with saline control rats [2].

1. Cepeda MS et al. Defining the therapeutic role of local anesthetic sympathetic blockade in complex regional pain syndrome: A narrative and systematic review. Clin J Pain 2002;18(4):216–33.

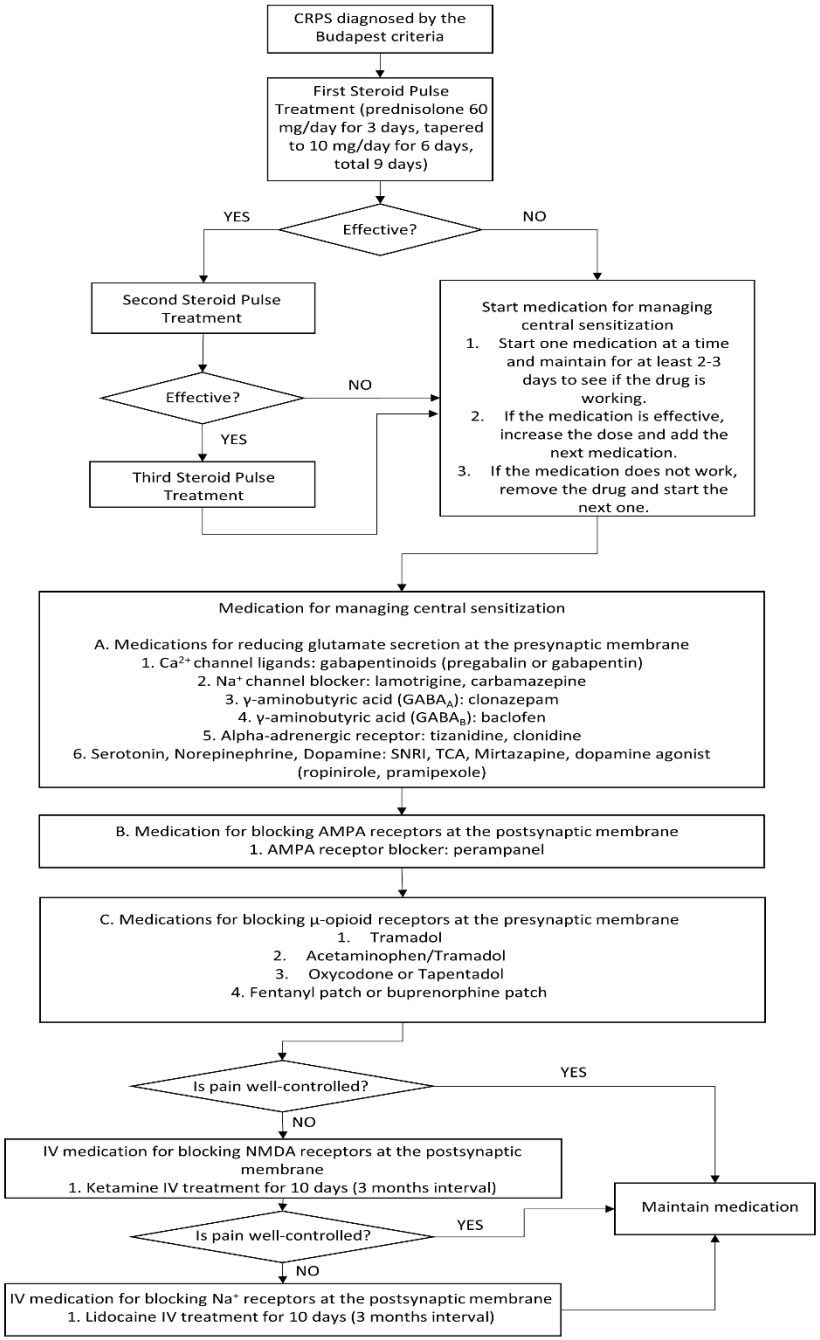
2. Lee SE, Kim JH. Involvement of substance P and calcitonin gene-related peptide in development and maintenance of neuropathic pain from spinal nerve injury model of rat. Neurosci Res 2007;58(3):245–9.

Ion channel in the sensory neuron



Increased number of Na+ Rc at injured Aδ & c-fiber

Algorithm of Multimodal Medication Therapy



Title: Experience from a Single-Center Study on Multimodal Medication Therapy for Patients with Complex Regional Pain Syndrome

Authors

Min Cheol Chang, M.D.[1], Jin-Woo Choi, M.D.[2], Donghwi Park, M.D., Ph.D.[2**]

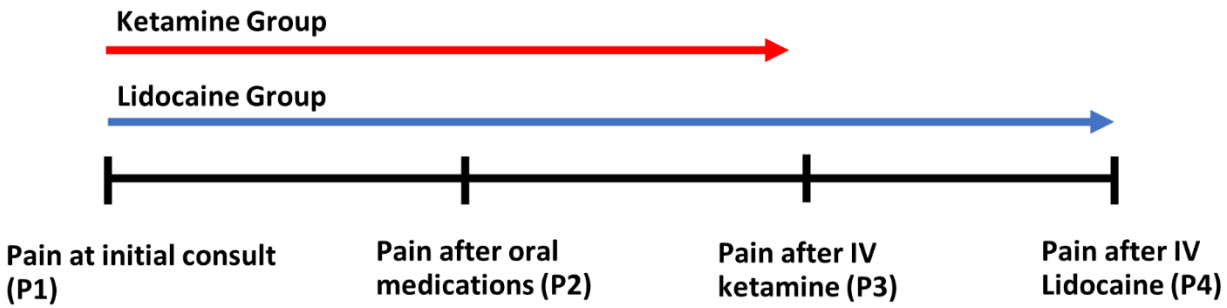
Affiliations

[1]Department of Rehabilitation medicine, Yeungnam University Hospital, Daegu 42415, Republic of Korea

[2]Department of Physical Medicine and Rehabilitation, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan 44033, Republic of Korea

Table 1. The characteristics of patients with CRPS in this study.

Group	Ketamine Group	Lidocaine Group	Total
Number	39	6	45
Age (years)	51.62±11.09	54.33±5.72	51.98±10.53
Sex (Male : Female)	21 : 18	4 : 2	25 : 20
Body weight (kg)	68.56±12.04	63.17±3.04	67.84±11.72
NRS at admission	8.26±1.49	8.75±1.08	8.32±1.44
NRS at discharge	5.20±1.30	5.83±0.68	5.29±1.24


Ketamine Group
Lidocaine Group
Pain at initial consult (P1)
Pain after oral medications (P2)
Pain after IV ketamine (P3)
Pain after IV Lidocaine (P4)

Group	Ketamine Group	Lidocaine Group	Total
Gabapentin (%)	5 (12.8%)	0 (0%)	5 (11.1%)
Gabapentin dose (mg)	1060±444.97 (400-1600)		1060±444.97 (400-1600)
Pregabalin (%)	31 (79.5%)	5 (83.3%)	36 (80%)
Pregabalin dose (mg)	326.61±152.88 (75-600)	210±82.16 (150-300)	310.42±149.93 (75-600)
Tramadol (%)	2 (5.1%)	0 (0%)	2 (4.4%)
Tramadol dose (mg)	150±70.71 (100-200)		150±70.71 (100-200)
Acetaminophen/Tramadol (%)	14 (35.9%)	2 (33.3%)	16 (35.6%)
Acetaminophen/Tramadol dose (mg)	91.07±24.23 (75-150)	75.00 ± 0.00 (75-75)	89.06±23.22 (75-150)
Perampanel (%)	22 (56.4%)	2 (33.3%)	24 (53.3%)
Perampanel dose (mg)	3.82±1.62 (2-8)	3.00±1.41 (2-4)	3.75±1.59 (2-8)
Clonazepam (%)	35 (89.7%)	4 (66.7%)	39 (86.7%)
Clonazepam dose (mg)	0.87±0.4 (0.25-2)	0.75±0.29 (0.5-1)	0.86±0.39 (0.25-2)
Diazepam (%)	4 (10.3%)	1 (16.7%)	5 (11.1%)
Diazepam dose (mg)	2.5±1.0 (2-4)	2.0 ±0.0(2-2)	2.4±0.89 (2-4)
Lorazepam (%)	13 (33.3%)	4 (66.7%)	17 (37.8%)
Lorazepam dose (mg)	0.65±0.43 (0.5-2)	3±1.15 (2-4)	1.21±1.20 (0.5-4)
Amitriptyline (%)	6 (15.4%)	0 (0%)	6 (13.3%)
Amitriptyline dose (mg)	9.17±2.04 (5-10)		9.17±2.04 (5-10)
Baclofen (%)	1 (2.6%)	1 (16.7%)	2 (4.4%)
Baclofen dose (mg)	30.0±0.0 (30-30)	20.0±0.0 (20-20)	25±7.07 (20-30)

Mean ± standard deviation (minimum value – maximum value).

Group	Ketamine Group	Lidocaine Group	Total
Duloxetine (%)	33 (84.6%)	1 (16.7%)	34 (75.6%)
Duloxetine dose (mg)	49.09±32.53 (30-120)	30.0±0.0 (30-30)	48.53±32.21 (30-120)
Mirtazapine (%)	13 (33.3%)	0 (0%)	13 (28.9%)
Mirtazapine dose (mg)	20.19±9.87 (7.5-30)		20.19±9.87 (7.5-30)
Oxycodone (%)	7 (17.9%)	2 (33.3)	9 (20%)
Oxycodone dose (mg)	12.86±4.88 (10-20)	20.0±0.0 (20-20)	14.44±5.27 (10-20)
Tapentadol (%)	5 (12.8%)	0 (0%)	5 (11.1%)
Tapentadol dose (mg)	160±89.44 (100-300)		160±89.44 (100-300)
Fentanyl patch (%)	15 (38.5%)	4 (66.7%)	19 (42.2%)
Fentanyl patch dose (μg)	28.1±13.46 (12-50)	50 (50-50)	28.76±16.36 (12-50)
Buprenorphine patch (%)	6 (15.4%)	0 (0%)	6 (13.3%)
Buprenorphine patch dose (μg)	6.67±2.58 (5-10)		6.67±2.58 (5-10)
Carbamazepine (%)	5 (12.8%)	0 (0%)	5 (11.1%)
Carbamazepine dose (mg)	400.0±0.0 (400-400)		400.0±0.0 (400-400)
Quetiapine (%)	9 (23.1%)	5 (83.3%)	14 (31.1%)
Quetiapine dose (mg)	148.61±148.62 (12.5-400)	147.5±76.24 (12.5-200)	148.21±124.02 (12.5-400)
Zolpidem (%)	7 (17.9%)	1 (16.7%)	8 (17.8%)
Zolpidem dose (mg)	10.0±0.0 (10-10)	6.25±0.0 (6.25-6.25)	9.53±1.33 (6.25-10)

Mean ± standard deviation (minimum value – maximum value).

	NRS score at P1	NRS score at P2	NRS score at P3	NRS score at P4	P-value between periods	
Ketamine group	9.83±0.33 (9-10)	8.32±1.52 (4-10)	5.20±1.30 (2-7.5)		P1-P2	<0.001*
					P2-P3	<0.001*
					P1-P3	<0.001*
Lidocaine group	9.83±0.41 (9-10)	8.75±1.08 (7.5-10)	8.42±1.28 (7-10)	5.83±0.68 (5-7)	P1-P2	0.048*
					P1-P3	0.026*
					P1-P4	<0.001*
					P2-P3	0.175
					P2-P4	<0.001*
					P3-P4	0.001*
Total	9.83±0.34 (9-10)	8.39±1.46 (4-10)	5.68±1.73 (2-10)	5.83±0.68 (5-7)	P1-P2	<0.001*
					P1-P3	<0.001*
					P1-P4	<0.001*
					P2-P3	<0.001*
					P2-P4	<0.001*
					P3-P4	0.001*

Mean ± standard deviation (minimum value – maximum value).
P<0.05 is considered to be statistically significant.

Summary

- Start steroid treatment as soon as possible !

- 환자마다 약에 대한 반응이 다를 수 있기 때문에, multi-modal medication 을 환자에게 설명과 더불어 환자의 통증 반응정도에 맞추어 적절히 사용하자.

- Intravenous ketamine or lidocaine 이 refractory neuropathic pain 에 중요한 치료중의 하나일 수 있다.

- 치료라기 보다는 manage 하는 질병이라는 것에 대한 교육 필요.

Case 1

예시: 56세 남자

4년 전 산재로 우측 하지의 수상. Sural nerve injury.

Lyrica, Enafon, Ultracet Semi, Fentanyl Patch, Celebrex 복용하고,

간헐적인 목에 SGB 시행하며 지냈으나 통증이 조절 안되어서 내원.

1. Steroid pulse treatment -> 효과 없음.
2. Lyrica 75mg bid 효과 -> 150mg bid dose up
3. Rivotril 0.5mg 1t 효과 -> 1t bid 로 dose up.
4. Baclofen, Sirdalud, Cymbalta 효과 없음.
5. Fycompa 2mg 효과 -> 5mg 증량 side effect -> 2mg 다시 감량.
6. Ketamine IV -> 효과, 3개월동안 효과 유지.
   3개월마다 입원하여 Ketamine IV 시행. NRS 3-4 유지.

Case 2, 3

예시: 40세 남자

한달 전 Deltoid 부위 TPI 후, 찌릿하면서 팔까지 저린 신경통증 발생.
진단위해 본원 내원. 손이 붓는 느낌, 땀도 많이 난다. 근전도에서 이상 없음.

1. Steroid pulse treatment -> 효과 있음. 3회까지 시행.

2. NRS 1-2 정도의 통증 남아 Neurontin 100mg bid 효과
   -> 300mg bid dose up 후 total improved.

예시: 36세 여자

이주일 전 엉덩이 NSAID 주사 후, 찌릿하면서 다리까지 저린 신경통증 발생.
진단위해 본원 내원. 발이 붓는 느낌. 근전도에서 이상 없음.

1. Steroid pulse treatment -> 효과 있음. 2회까지 시행.

2. NRS 1-2 정도의 통증 남아 Neurontin 100mg bid 후 nearly total improved.

Case 4

예시: 64세 남자

5년 전 전기감전을 당한 후 CRPS 발생.

SCS 까지 하였으나 통증이 재발하여 다시 통증 조절위해 내원함.

통증으로 인해 만성알콜중독. 정신과 다니는 중.

1. Steroid pulse treatment -> 효과 없음.
2. Lyrica 75mg bid 효과 -> 150mg bid dose up
3. Rivotril, Baclofen, Sirdalud, Cymbalta 효과 없음.
4. Fycompa 효과없음.
5. Ultracet Semi ER 효과 -> Ultracet ER 로 증량.
6. Ketamine IV + midazolam IV for 10 days->필름이 끊기면서 병동에서 난동
7. Lidocaine IV without midazolam for 10 days
   NRS 10 -> 5로 조절양상 (한달~두달정도 유지)

Thanks for Your Attention!